May 20, 2005

Timothy Adams, Ph.D.
Technical Contact
International Association of Color Manufacturers
HPV Committee
1620 I Street, N.W.
Suite 925
Washington, DC 20006

Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Sunset Yellow posted on the ChemRTK HPV Challenge Program Web site on March 30, 2004. I commend the International Association of Color Manufacturers HPV Committee for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Committee advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: M. E. Weber
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Sunset Yellow

Summary of EPA Comments

The sponsor, the International Association of Color Manufacturers (IACM), submitted a test plan and robust summaries to EPA for Sunset Yellow (FD&C Yellow No. 6; C.I. Food Yellow No. 3; CAS No. 2783-94-0) dated March 10, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on March 19, 2004. Information is also submitted on FD&C Red No. 40, C.I. Acid Red No. 14, stilbene sulfonic acid derivatives, and C.I. Acid Yellow 23, as analogs. [CAS Numbers for these analogs are not provided.]

EPA has reviewed this submission and has reached the following conclusions:

1. Analog Justification. EPA disagrees with the submitter's proposal to use certain other azo dyes and stilbene sulfonic acid derivatives as representative compounds for the sponsored chemical.

2. Physicochemical Properties. The data submitted for these endpoints are adequate for the purposes of the HPV Challenge Program.

3. Environmental Fate. The submitter needs to provide the measured ready biodegradation data on the sponsored chemical, include technical discussion on stability in water in the robust summary, and provide the input values for parameters used in the Level III fugacity robust summary.

4. Health Effects. Adequate data are available for the acute, repeated-dose, and genetic toxicity endpoints for the purposes of the HPV Challenge Program. The data submitted for the reproductive toxicity endpoint are inadequate. EPA reserves judgement on the adequacy of the data submitted for developmental toxicity pending submission of critical study information. Testing is needed to address reproductive (and possibly developmental) toxicity. The submitter also needs to address deficiencies in the robust summaries.

5. Ecological Effects. Ecological endpoints have not been addressed adequately for the purposes of the HPV Challenge Program. The submitter needs to provide data for all endpoints on the sponsored chemical.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Sunset Yellow Challenge Submission

Analog Justification

The test plan provided analog data to address or support the direct photodegradation, biodegradation, aquatic toxicity, and *in vivo* genetic toxicity endpoints; however, it did not provide any rationale supporting these analogs.

EPA disagrees with the submitter that the stilbene sulfonic acid derivatives proposed to supply data for the acute fish and invertebrate toxicity endpoints are appropriate analogs for the sponsored chemical. All the stilbene analogs lack the –N=N– linkage, the phenol function, and the naphthalene group of the sponsored substance, and contain amino or nitro groups not present in the sponsored chemical.

Although Acid Red 14 has some similarity to the sponsored chemical, its adequacy as an analog is moot because the cited biodegradation data are inadequate as noted below.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided for photodegradation are adequate for the purposes of the HPV Challenge Program.

Stability in water. While EPA agrees that Sunset Yellow does not contain water-sensitive functional groups, the submitter needs to add a brief technical discussion of this point to the robust summary.

Biodegradation. The biodegradation data are not adequate for the purposes of the HPV Challenge Program. The BIOWIN-estimated data are not adequate in place of measured data. The facts do not sustain the submitter's argument–based on data from a non-standard (only 24-hr) test on proposed analog Acid Red 14–that the test substance will not biodegrade because it does not adsorb to sludge. Although Acid Red 14 does not biodegrade under the conditions of the test, several other structurally related dyes mentioned in Shaul *et al.* 1991 are readily biodegradable but do not appear to adsorb to sludge under similar test conditions. The submitter needs to provide measured ready biodegradation data for Sunset Yellow following OECD TG 301.

Fugacity. The submitter needs to include the input values for parameters used in the Level III estimation in the robust summary.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for the acute, repeated-dose, and genetic toxicity endpoints for the purposes of the HPV Challenge Program. The data submitted for the reproductive toxicity endpoint are inadequate. EPA reserves judgement on adequacy of the data submitted for the developmental toxicity endpoint. Testing will be needed to address the reproductive and possibly the developmental toxicity. The submitter needs to address deficiencies in the robust summaries.

Reproductive toxicity. The submitted 3-generation reproductive toxicity study in rats is not adequate. The maximum dose tested, 500 mg/kg/day, was much lower than the OECD guideline-required dose level of 1000 mg/kg/day, and no systemic toxicity was shown in the parental animals. In addition, critical information was missing from the robust summary, including the purity of the test material, the experimental design (especially the timing of exposure with respect to mating and termination), and the parental and fetal endpoints examined. A combined reproductive/developmental toxicity screening test will be needed following OECD TG 421 (see following comments).

Developmental toxicity. EPA was unable to determine the adequacy of the submitted teratogenicity study in rats because of insufficient study details in the robust summary. Critical information missing included the purity of the test material and the maternal and fetal endpoints that were examined, such as the litter size, weight, and sex, number of fetuses examined for external, skeletal and visceral alterations, gravid uterine weights, number of corpora lutea, number of implantations, and statistical significance of any reported findings. The submitter needs to provide the above information to allow an independent assessment of study adequacy and the validity of the stated NOAEL and LOAEL. If the additional information is not available, a combined reproductive/developmental toxicity screening test (OECD TG 421) will satisfy this endpoint.

Ecological Effects (fish, invertebrates, and algae)

Acute toxicity to fish, invertebrates, and *algae*. The submitter provided aquatic toxicity data only for proposed analog chemicals that, as stated above, are not adequately similar to the sponsored chemical, or are incompletely identified (algal test). The ECOSAR values for the sponsored chemical are not appropriate because the ECOSAR model does not yet include a calculation for anionic dyes. Therefore, all three acute aquatic toxicity tests are needed on the sponsored chemical following OECD Test Guidelines.

The references provided for acute fish and invertebrate toxicity in the test plan text (Greim et al, 1994) do not match those in the robust summaries. In addition, the last structure in Table 3 of the test plan does not match the name provided, 2,2'-(1,2-ethenediyl)bis(5-aminobenzenesulfonic acid), dipotassium salt (the molecular structure shows nitro substituents while the name specifies amino groups).

Specific Comments on the Robust Summaries

Human Health Effects

Acute toxicity. Information missing from one or more of the robust summaries of the oral studies in rats and mice includes the purity of the test material, animal data (e.g., age and weight), dose levels tested, and method of LD_{50} calculation.

Repeated-dose toxicity. The robust summaries for the NTP 12-week (range-finding) dietary studies in rats and mice do not contain information on the specific hematology, clinical chemistry and urinalysis parameters that were examined, nor the specific organs that were weighed or examined for gross and microscopic pathology.

Genetic toxicity. *Gene mutations.* Information missing from a robust summary of an Ames test (Chung et. al., 1981) includes the purity of the test substance, test concentration levels (as opposed to a dose range), culture conditions (e.g., temperature and medium used), duration of incubation, number of colonies counted per concentration, the source of the metabolic activation system, responses to positive controls, whether or not testing was conducted both with and without metabolic activation and the results of each of these test conditions, statistical methods used and the results of statistical analyses.

Chromosomal aberrations. Information missing from a robust summary of an *in vitro* chromosomal aberrations study (Ishidate *et al.*, 1984) includes test guideline/standardized method used, culture conditions (e.g., incubation temperature), actual test concentrations, and results of statistical analyses.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.